

Supplementation with Bio-Calcium from Shells *Pinctada Maxima* in Postmenopausal Women with Decreased Mineral Bone Density – Pilot Study

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SUMMARY

Introduction Treatment of osteoporosis, in addition to a specific antiresorptive or anabolic treatment, requires supplementation with calcium and vitamin D. Widespread cultivation of pearl shells has made pearls available for commercial use for a very reasonable price. The main chemical compound of pearls from shells *Pinctada maxima* is calcium-carbonate (CaCO₃). Recently developed technologies applied in a micronisation process have provided increased gastrointestinal resorption of calcium, estimated at over 90% of calcium intake.

Objective The paper is aimed at monitoring of efficacy and tolerance of six-month bio-calcium supplementation in postmenopausal women with reduced bone mineral density.

Methods Group I (30 patients) received, three times a day, capsules of pearl powder from shells *Pinctada maxima* (it is equal to 260 mg of elementary calcium); group II (20 patients) received a daily dose of 500 mg inorganic CaCO₃. Both groups received 666 IU of cholecalciferol per day. In all patients, bone mineral density (BMD) of the spine or hip, serum blood and urine levels of Ca, phosphates and alkaline phosphatase, were measured before and after six months of the treatment.

Results Group I/Group II: average age 61.7/61.7 years; beginning of menopause: 48.32 /48 years; menopause duration 13.4/13.7 years; average body mass index 27.2/27 kg/m². These two groups did not differ significantly before supplementation. Six-month supplementation with CaCO₃ of the biological origin led to the increase of BMD from 0.901 g/cm² to 0.948 g/cm² (p=0.067), while BMD remained the same in the group supplemented with inorganic CaCO₃. Gastrointestinal tolerability of bio-calcium was excellent, without any adverse events.

Conclusion These data could not strongly support the hypothesis of better efficacy of bio-calcium taking into account a small number of patients and a short follow-up period in this pilot study. Tolerance of CaCO₃ of the biological origin was excellent and free of any adverse events. The results of laboratory values were within normal range.

Key words: calcium supplementation; bio-calcium; inorganic calcium; osteoporosis; *Pinctada maxima*

INTRODUCTION

The role of calcium – the main component of the bone mass – in prevention and treatment of osteoporosis has been extensively studied [1-8]. The recommendations on advised calcium (Ca) intake are generally available, with the tendency of dose increasing in comparison to the previous decades with limitation of the upper cutoff value in order to prevent adverse events [3, 4]. The results suggest positive effect of calcium supplementation on the skeletal growth and peak bone mass in prepubertal girls, particularly those with previously low calcium intake [5]. Calcium and vitamin D supplementations are significant in prevention of early postmenopausal bone mass loss [6].

However, in spite of the fact that calcium intake has been widely accepted as a risk factor for future fractures, the results of the studies carried out so far are controversial. Thus, a meta-analysis performed by Kanis et al has failed to demonstrate the association between low calcium intake (less than 1 cup of milk per day) and a significant increase of risk from osteoporotic fractures in later life [7]. In the light of great economic burden related to osteoporotic fractures and having in mind low costs of combined vitamin D and

calcium supplementation, it appears to be justifiable from the economic point of view [8].

Calcium supplements are available in numerous forms, most commonly as calcium citrate and calcium carbonate (CaCO₃). Molluscs *Pinctada maxima* may serve as a good source of natural bio-calcium intended for supplementation. Emerging of pearl shell nurseries in a number of countries in the world has made them commercially available for wide use at a relatively low cost [9].

The low level of pearl powder absorption has always been problematic since the special structure of the pearls makes the release of the nutrients from the pearls difficult. The problem has been overcome by a novel, unique technology developed by pharmaceutical companies (Physical Ultra Fine Technology – PUFT), which enabled disintegration of the pearl powder to nanomolar pearl particles (Nanometer Pearl Powder – NPP). Manufacture of capsules with fine pulverized pearls of 40-80 nm in diameter has enabled 100% preservation of natural ingredients of the pearl powder with an enormous increase of pearl powder's specific surface area (SSA), which has improved significantly bioavailability of the preparation with bioactive calcium absorption of 90-95%.

OBJECTIVE

The paper is aimed at monitoring of efficacy and tolerance of six-month bio-calcium supplementation in postmenopausal women with reduced bone mineral density.

METHODS

The prospective study included 50 female outpatients treated at the Institute of Rheumatology in Belgrade, Serbia diagnosed with reduced spinal or hip bone density (osteopenia or osteoporosis). Bone mineral density (BMD) is measured on the lumbar spine (L) or hip according to the DXA method (Double Energy X-ray Absorption) using the Lunar DPX device.

The inclusion criteria were the following: female sex, menopausal status (either natural or artificially-induced menopause), T index of the measured region with standard deviation (SD) from -1 to -3, patients previously untreated with other therapeutic approaches for osteoporosis (antiresorptive and/or substitution). The study also included the patients in whom other specific osteoporosis treatments were indicated. However, they refused to comply with them.

Exclusion criteria included all forms of secondary osteoporosis, high risk of development of fractures, administration of drugs with adverse effects on bone density (diuretics, anticonvulsives, heparin, corticosteroids), severe infections, malignant diseases or other conditions rendering the patients unsuitable for treatment based on the investigator's judgment.

Randomization of patients was made by drawing of numbers from 1-50, with patients identified with numbers from 1-30 allocated to a group to be subjected to substitution therapy with pearl calcium Biser® (Zhejiang Fenix Pharmaceutical Co, Ltd. PR of China), 3×1 capsule per day, corresponding to 260 mg of elemental bio-CaCO₃ per day. Biser® 250 mg capsules were granted marketing authorization for the territory of Serbia by Sanitary Inspectorate of the Republic of Serbia. The capsules were analysed at the School of Pharmacy, University of Belgrade (Institute of Bromatology).

The second group of patients identified with numbers 31-50 (20 patients) was supplemented with inorganic Kalcijum karbonat® (Alkaloid, Skopje) 1.250 mg once a day (500 mg of elemental calcium). Both groups were administered 666 IU of cholecalciferol per day (Vigantol®, Merck). The study was approved by the Ethics Committee of the Institute of Rheumatology in Belgrade. All the patients were properly

informed and gave their informed consents for inclusion into the study before application of any medical procedures.

Before the commencement of supplementation, laboratory tests were performed including serum calcium, phosphorus and alkaline phosphatase and 24-h urine calcium and phosphorus according to the spectrophotometric method using biochemical analyzers. After completion of six-month supplementation of calcium and vitamin D₃, the DXA examination of the same skeletal region was performed by the same investigator and follow-up laboratory tests of the same parameters as at the baseline were performed. Tolerance of supplementation and onset of adverse events were monitored.

The prospective follow-up lasted for 6 months and the study was carried out in the period early November 2006 – end of December 2007.

Basic descriptive statistical methods were used (mean value, standard deviation, range of values, median). The significance of the obtained results was analysed by the Student's t-test for dependent samples, where the difference was considered to be significant at $p < 0.05$.

RESULTS

Characteristics according to groups before initiation of supplementation

Group I patients (n=30) were aged 61.7 (45-78) at the average. The menopause started at the age of 48.3 (36-55) and lasted for 13 (1-27) years. Previous bone fractures were not evidenced in 23 (76.7%) patients, while previous fractures were recorded in 7 (23.3%) patients: Colles' fractures of the radius in 3 patients, lumbar vertebral fractures in 1 patient, rib and metatarsal bone fractures in one patient each. The average body mass was 67.7 (51-92) kg, average height 159.8 (147-173) cm. In majority of the patients (26/86.7%) BMD was measured in the lumbar spine, while in 4 (13.3%), it was measured in the hip. The average bone mineral density before supplementation was 0.901 (range 0.736-1.033) g/cm², with T index being -1.90 (range -3 to -1.2) SD (Table 1).

The average serum calcium value was 2.3 (2.0-2.62) mmol/l, phosphorus 1.2 (0.8-1.5) mmol/l, and alkaline phosphatase 68.6 (39-100) IU/l. The average calciuria in 24-h urine was 0.18 (0.02-0.43) g/24 h, while phosphaturia was 0.59 (0.1-1.2) g/24 h (Table 2).

The average age of Group II patients (n=20) was the same - 61.7 (46-76) years. The menopause commenced in

Table 1. General patients' indicators

Parameters	Group I	Group II	p
Age (years)	61.7±8.3 (45-78)	61.7±8.6 (46-76)	0.5
Onset of menopause (years)	48.3±3.9 (36-55)	48±3.3 (42-54)	0.38
Duration of menopause (years)	13.4±7.3 (1-27)	13.7±9.5 (2-33)	0.447
Fractures (number)	No	23 (76.7%)	
	Yes	7 (23.3%)	
Body weight (kg)	67.7±10.3 (51-92)	71.1±9.7 (52-90)	0.140
Body height (cm)	159.8±6.2 (147-173)	162.2±3.4 (157-169)	0.08
Body mass index (kg/m ²)	27.2±3.2 (21.9-33)	26.9±4.1 (19.3-32.3)	0.289

Table 2. Laboratory parameters according to groups before and after six-month supplementation

Parameters		Group I	Group II	p
Serum calcium	Before	2.3±0.16	2.3±0.18	0.292
	After	2.3±0.12*	2.3±0.13**	
Serum phosphorus	Before	1.2±0.2	1.2±0.17	0.470
	After	1.2±0.19*	1.2±0.08**	
Alkaline phosphatase	Before	68.6±15.2	69.1±18.9	0.461
	After	64.2±11.9*	60.7±21.3**	
Urine calcium	Before	0.18±0.1	0.21±0.15	0.218
	After	0.26±0.3*	0.28±0.2	
Urine phosphorus	Before	0.59±0.3	0.65±0.36	0.201
	After	0.62±0.2*	0.58±0.29**	

* 3 patients lost for follow-up;

**3 patients lost for follow-up; 1 patient refused blood taking, urine analyses were performed

Laboratory test changes after 6 months in comparison to baseline values:
Group I: serum Ca p=0.219; serum P p=0.467; alkaline phosphatase p=0.235; urine Ca p=0.168; urine P p=0.796;
Group II: serum Ca p=0.702; serum P p=0.909; alkaline phosphatase p=0.458; urine Ca p=1.3; urine phosphorus p=0.408

this group at the age of 48 (42-54) and lasted 13.7 (2-33) years. Majority of the patients (15/75%) were free of bone fractures, while previous bone fractures were present in 5 (25%) patients: radius and lower leg fracture in the first one, lumbar vertebral fracture in the second, two fractures of the radius in the third, radius fracture in the fourth, while multiple fractures were evidenced in the fifth patient. Their average body mass was 71 (52-90) kg, height 162 (157-169) cm, and BMI 27 (19.3- 32.3) g/m² (Table 1).

In 16 (80%) patients, BMD was measured on the lumbar spine, while in 4 (20%), it was measured on the hip. The average bone density was 0.913 (0.632-1.03) g/cm², while T index was -1.90 (from -3 to -1.32) SD (Table 3).

The average blood calcium value was 2.3 (2.0-2.8) mmol/l, phosphorus 1.2 (range 0.9 - 1.7) mmol/l, alkaline phosphatase approximately 69 (29.4-107) IU. The average calciuria measured in 24-h urine was 0.21 (0.04-0.5) g/24 h, with phosphaturia being 0.65 (range 0.3 - 1.3) g/24 h (Table 2).

None of the observed parameters (age, onset and duration of menopause, body mass, height, BMI, BMD and T-score values or laboratory indicators) did not differ significantly between the two groups before supplementation.

Results after six-month supplementation

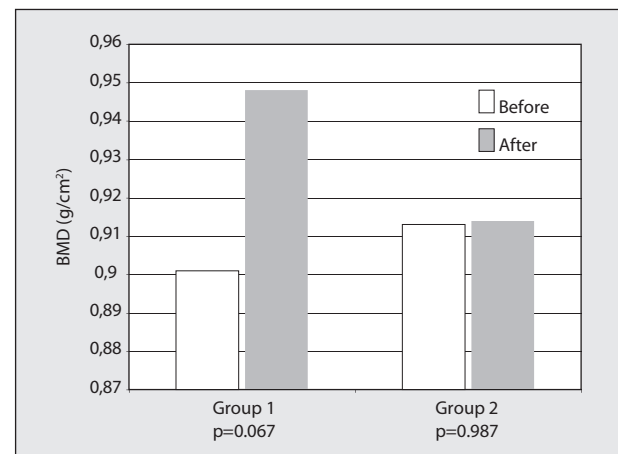
Out of 30 patients of group I, six-month supplementation was completed in 27 patients. Based on the physician's decision, 2 patients were excluded: one due to scheduled gastrointestinal investigations, and the other for non-compli-

Table 4. Tolerance and adverse events by the end and during six-month treatment

Parameters		Group I	Group II
Tolerance after 6 months	Good	27/27 (100%)	14/17 (82.3%)
	Poor	-	3/17 (17.6%)
Adverse events 0-6 months	Absent	29/30 (97%)	15/20 (75%)
	Present	1/30 (3.3)*	5/20 (25%)**

* One patient reported weight gain

** Two patients reported dyspepsia: nausea, bloating, abdominal pain; one reported rapid heart beats; other two patients discontinued treatment due to adverse events

**Graph 1.** Bone mineral density before and after 6-month supplementation

ance with Ca/vitamin D₃ schedule. The third patient left the study based on her own decision. None of the patients lost for further follow-up reported adverse events in the course of supplementation (Table 4).

BMD increase in the measured region from 0.901 to 0.948 g/cm² was evidenced in this group, which is close to the significance limit (p=0.067), as well as reduced negativity of T index from -1.9 to -1.7 (p=0.179) (Table 3, Graph 1).

Mean blood values of calcium 2.4 (2.2-2.4), phosphorus 1.2 (0.88-1.67) and alkaline phosphates 64.2 (46.9-84.5) did not differ significantly in comparison to the baseline values. Moreover, no significant changes in calciuria (0.26) and phosphaturia (0.62) in 24-h urine were detected (Table 2).

Good tolerance of pearl calcium was recorded in all 27 patients who completed six-month follow-up. In the course of a six-month follow-up, one of the patients (3.7%) reported an adverse event manifested as increase of body weight (Table 4). No new fractures were evidenced in this period.

A six-month treatment was completed in 17 out of 20 included patients of group II. One of the patients left the

Table 3. Bone mineral density according to groups

Parameters		Group I	Group II	p
DXA (number)	Lumbar spine	26 (86.7%)	16 (80%)	
	Hip	4 (13.3%)	4 (20%)	
BMD (g/cm ²)	Before supplementation	0.901±0.088 (0.74-1.03)	0.913±0.101 (0.63-1.03)	p=0.332§
	After 6 months	0.948±0.109 (0.68-1.11)*	0.914±0.128 (0.69-1.04)#	
T-score (SD)	Before supplementation	-1.9±0.42 (-3 to -1.2)	-1.9±0.72(-3.1 to -1.32)	p=0.303§
	After 6 months	-1.7±0.481 (-3 to -1.1)**	-1.9±0.72 (-3.1 to -1.32)##	

* BMD before and after 6-month treatment p=0.067; ** T-score before and after 6-month treatment t test p=0.179;

BMD before and after treatment p=0.987; ## T-score before and after treatment p=0.725; § between the groups before commencement of treatment

study based on her own decision, while the other 2 were excluded due to the onset of adverse events. The first patient was excluded 10 days after the commencement of supplementation due to gastric pains, nausea and vomiting while the second was excluded after 3 months since she reported vitamin D intolerance (persistent diarrhoeas following each administration of the drops) (Table 4).

An increase of bone mineral density was practically not recorded in this group (BMD at baseline 0.913, by the end of follow-up 0.914; $p=0.987$) or T-score change (-1.9 at baseline and at the end of follow-up) (Table 3, Graph 1).

Significant changes of laboratory and urine blood parameters were not recorded in this group either. Mean value of blood calcium was 2.3 (2.1-2.43) mmol/l, phosphorus 1.2 (1.1-1.3) mmol/l and alkaline phosphatase 60.7 (45.7-74.8) IU. Moreover, calciuria increase from 0.21 to 0.28 g/24 h was not statistically significant or decrease of phosphaturia value in g/24 h (Table 2).

Good tolerance was recorded in 14 out of 17 patients who completed six-month supplementation. Lack of tolerance in the form of nausea, bloating and gastric pains was reported by 2 patients, while the third one reported rapid heart beats. With 2 patients withdrawn from the study when adverse events are taken into account, the total number of patients who developed adverse events over the 6-month follow-up was 5 out of 20 (25%) patients (Table 4). No new fractures were recorded in this group either.

DISCUSSION

The long-term process of treatment of osteoporosis necessitates, in addition to specific antiresorptive therapy, calcium and vitamin D supplementation. Investigators from Denmark reported, in ~10,000 individuals aged ≥ 66 , living independently, significant (16%, $p<0.025$) reduction of risk fractures in case of the application of calcium and vitamin D supplementation [10].

We are aware that assessment of efficacy after 6 months is a short period to achieve BMD to be documented by the DXA method. However, our results indicate the increase of bone mineral density as early as after six months after administration of biological CaCO_3 in postmenopausal women with reduced bone density. No changes of bone density were recorded after 6-month supplementation in the group receiving twice as high inorganic CaCO_3 dose.

Tolerance of bio-calcium supplementation was excellent in absence of any adverse events with good adherence to treatment. The information was highly significant, having in mind our own experience, and reference literature data, reporting that particularly poor compliance was associated with calcium/vitamin D supplementation, which emphasized the need for finding the new routes of supplementation [11].

Giant seashells *Pinctada maxima*, similarly to other members of *Pinctada* genus produce large pearls throughout their life. Both, pearl and mother-of-pearl, are basically composed of CaCO_3 (aragonite), while the bone is mostly composed of calcium phosphate (hydroxyapatite, HA) [9, 12]. The process of shell bio-mineralization has not been

completely elucidated yet. Organic calcium mostly originates from plankton used by shells for their nourishment, while pearl composition depends on the composition and temperature of seawater [13]. Initially formed meshwork of the organic matrix induced formation of crystals within the allowed space, which necessitates a continuous supply with calcium, with its uptake, active transport, accumulation and particularly regulatory processes of the mechanism still being an attractive field of research [12, 13].

By far more intriguing from the mineral part of the pearl is the organic one, which makes 2-8% of their content [10]. These two pearl components are arranged in several hundreds of closely, alternatively related layers [9, 13]. Phylogenetically highly distinct mechanisms of pearl and bone mineralization still have a common characteristic – both are the products of living organism bio-mineralization. The studies carried out so far have indicated that the pearl matrix has numerous diffusible, water-soluble proteins and growth factors (Water-Soluble Matrix-WSM) controlling both *in vivo* and *in vitro* the process of pearl bio-mineralization based on the mechanism similar to osteogenesis, i.e., HA synthesis in human population [9, 13, 14]. Previous studies have provided solid evidence that nacre produced by shell *Pinctada maxima* may stimulate osteoblast culture both, *in vivo* and *in vitro*, to produce bone (osteogenic activity), which makes it a suitable material for bone reparation [9, 13, 14]. *In vitro* studies support the initial hypothesis suggesting that diffusible signaling molecules of the shell nacre organic matrix are included in stimulation of mammalian osteoblasts – targeted cells in the process of bone synthesis [15]. Increased activity of alkaline phosphatase (osteoblast differentiation marker) has been documented in osteoblast and WSM culture as well as the increased quantity of antiapoptotic pro-oncogen Bcl-2 in the osteoblast cytoplasm and nucleus. It has also been evidenced that calmodulin - intracellular calcium sensor protein – actively participates in calcium transport, aimed at its deposition in the matrix meshwork as well as that only two amino acid residues in its structures have been changed during evolution from molluscs to vertebrata [12, 16].

Wide dental application of the alveolar implants made of natural calcium carbonate (bioracine) obtained from shells *Pinctada maxima* has evidenced that the chips may be implanted in human bone, accepted by the human body to express biological response through release of the active molecules that induce bone regeneration. The response included local osteogenetic activity and nacre integration into the host bone in absence of inflammatory reaction. Histological studies have evidenced unusual cellular fusion of the two types of tissue on the junction between the alveolar implants and human maxillary bone [17].

CONCLUSION

Six-month supplementation with CaCO_3 of the biological origin in the daily dose of 260 mg has led to the increase of bone mineral density from 0.901 g/cm² to 0.948 g/cm² ($p=0.067$), while bone mineral density remained the same

in the group supplemented with inorganic CaCO₃ in the daily dose of 500 mg. However, these data could not strongly support the hypothesis of better efficacy of bio-calcium taking into account a small number of patients and a short follow-up period in this pilot study.

Tolerance of CaCO₃ of the biological origin was excellent and free of any adverse events.

The results of laboratory calcium, phosphorus and alkaline phosphatase blood tests as well as calcium and phosphorus urine levels were within normal cutoff values.

NOTE

The results of this paper were presented as oral or poster presentation at: Meeting of the Physicians of Vojvodina, Kanjiza Spa 27/3/2008; 27th Timok's Medical Days, Zajecar, May 22-24, 2008; The Annual Meeting of Rheumatologists of the Republic of Serbia, Ivanjica, September 26, 2008; ICOBR 2008 - International Conference on Osteoporosis and Bone Research 2008, China, Beijing, October 22-25, 2008. Abstract has been published in Bone 2008; 43(Suppl 1):A67.

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Суплементација биолошким калцијумом из шкољке *Pinctada maxima* код жена у постменопаузи са смањеном минералном густином кости: пилот-студија

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КРАТАК САДРЖАЈ

Увод Лечење остеопорозе, уз специфичну антиресорптивну или анаболичку терапију, захтева суплементацију калцијумом и витамином Д. Главни састојак бисера шкољке *Pinctada maxima* је калцијум-карбонат (CaCO_3). Технологијом микронизације бисера у наномоларни прах повећана је гастроинтестинална апсорпција калцијума до више од 90% узете дозе. Култивација бисерних шкољки их је учинила опште доступним по врло приступачној цени.

Циљ рада Циљ истраживања је био да се установе ефикасност и подношљивост суплементације биолошким калцијумом код жена у постменопаузи са смањеном минералном густином кости (енгл. *bone mineral density* – *BMD*).

Методe рада Мерени су *BMD* кичме или кука и концентрације алкалне фосфатазе, калцијума и фосфора у серуму и 24-часовном урину пре и шест месеци после суплементације. Испитанице су сврстане у две групе: прву је чинило 30 жена које су примале суплементацију CaCO_3 у виду капсула бисерног праха шкољки *Pinctada maxima* (одговара 260 *mg* елементарног калцијума), а другу групу 20 жена које су примале неоргански CaCO_3 (500 *mg* елементарног калцијума). Обе групе су примале исту дневну дозу холекалциферола (666 ИЈ).

Резултати Просечна старост испитаница две групе била је иста – 61,7 година. На почетку менопаузе испитанице прве групе су у просеку имале 48,3 године, а испитанице друге групе 48 година. Менопауза је у просеку трајала 13,4 године код испитаница прве групе, а 13,7 година код испитаница друге групе. Просечна вредност индекса телесне масе у првој групи била је 27,2 *kg/m*², а у другој 27 *kg/m*². Групе су се по свим параметрима могле поредити ($p > 0,05$). *BMD* се код жена прве групе након шест месеци повећала са 0,901±0,088 на 0,948±0,109 *g/cm*² ($p=0,067$), док у другој групи није забележена промена *BMD*. Биолошки CaCO_3 испитанице су одлично поднеле и није било нежељених реакција.

Закључак Резултати ове пилот-студије не могу чврсто да подрже хипотезу о бољој ефикасности суплементације биолошким калцијумом у односу на неоргански, будући да је број испитаника био мали, а период посматрања кратак. Ипак, установљена је одлична подношљивост CaCO_3 биолошког порекла, а нежељених реакција није било. Сви лабораторијски показатељи у обе групе испитаница били су у границама нормалних вредности.

Кључне речи: суплементација калцијумом; биолошки калцијум; неоргански калцијум; остеопороза; *Pinctada maxima*